Eur J Pediatr (2016) 175:1267–1276
DOI 10.1007/s00431-016-2765-z

REVIEW

The changing face of dietary therapy for epilepsy

Ludovica Pasca[1] · **Valentina De Giorgis**[1,2] · **Joyce Ann Macasaet**[3] · **Claudia Trentani**[4] · **Anna Tagliabue**[4] · **Pierangelo Veggiotti**[1,2]

Received: 22 March 2016 / Revised: 7 August 2016 / Accepted: 19 August 2016 / Published online: 1 September 2016

Abstract Ketogenic diet is an established and effective non-pharmacologic treatment for drug-resistant epilepsy. Ketogenic diet represents the treatment of choice for GLUT-1 deficiency syndrome and pyruvate dehydrogenase complex deficiency. Infantile spasms, Dravet syndrome and myoclonic-astatic epilepsy are epilepsy syndromes for which ketogenic diet should be considered early in the therapeutic pathway. Recently, clinical indications for ketogenic diet have been increasing, as there is emerging evidence regarding safety and effectiveness. Specifically, ketogenic diet response has been investigated in refractory status epilepticus and encephalopathy with status epilepticus during sleep. New targets in neuropharmacology, such as mitochondrial permeability transition, are being studied and might lead to using it effectively in other neurological diseases. But, inefficient connectivity and impaired ketogenic diet proposal limit ideal availability of this therapeutic option. Ketogenic diet in Italy is not yet considered as standard of care, not even as a therapeutic option for many child neurologists and epileptologists.

Conclusions: The aim of this review is to revisit ketogenic diet effectiveness and safety in order to highlight its importance in drug-resistant epilepsy and other neurological disorders.

Communicated by Beat Steinmann

✉ Pierangelo Veggiotti
pierangelo.veggiotti@unipv.it

Ludovica Pasca
ludovica.pasca01@universitadipavia.it

Valentina De Giorgis
valentina.degiorgis@yahoo.it

Joyce Ann Macasaet
jamacasaet@gmail.com

Claudia Trentani
claudia.trentani@unipv.it

Anna Tagliabue
anna.tagliabue@unipv.it

[1] Department of Child Neurology and Psychiatry, IRCCS "C. Mondino" National Neurological Institute, Pavia, Italy

[2] Brain and Behaviour Department, University of Pavia, Via Mondino, 2, 27100 Pavia, Italy

[3] Makati Medical Center, Manila, Philippines

[4] Human nutrition and eating disorder center, department of public health, experimental and forensic medicine, University of Pavia, Pavia, Italy

What is Known:
- *Ketogenic diet efficacy is now described in large case series, with adequate diet compliance and side effects control.*
- *Ketogenic diet is far from being attempted as a first line therapy. Its availability varies worldwide.*

What is New:
- *New pharmacological targets such as mitochondrial permeability transition and new epileptic syndromes and etiologies responding to the diet such as refractory status epilepticus are being pointed out.*
- *Ketogenic diet can function at its best when used as a tailor-made therapy. Fine tuning is crucial.*

Keywords Ketogenic diet · Drug-resistant epilepsy · GLUT1DS ketones · Modified Atkins diet · Dietary therapy

Abbreviations

AEDs	Antiepileptic drugs
CAU	Care as usual
DRE	Drug-resistant epilepsy
DS	Dravet syndrome

ESES	Encephalopathy with status epilepticus during sleep
FE	Focal epilepsy
FIRES	Fever-induced refractory epileptic encephalopathy
GI	Gastrointestinal
GLUT1DS	GLUT-1 deficiency syndrome
HDL-C	HDL cholesterol
ILAE	International League Against Epilepsy
IS	Infantile spasms
KD	Ketogenic diet
LBD	Lafora body disease
LDL-C	LDL cholesterol
LGIT	Low glycemic index treatment
LKS	Landau-Kleffner syndrome
MAD	Modified Atkins diet
MAE	Myoclonic-astatic epilepsy
MCT	Medium-chain triglyceride diet
MD	Mitochondrial disorders
mPT	Mitochondrial permeability transition
PDCD	Pyruvate dehydrogenase complex deficiency
RSE	Refractory status epilepticus
SSP	Subacute sclerosing panencephalitis
TSC	Tuberous sclerosis complex
VNS	Vagal nerve stimulation
VPA	Valproic acid

Introduction

Current International League Against Epilepsy (ILAE) defines drug-resistant epilepsy (DRE) as 'failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs (AEDs) schedules to achieve sustained seizure freedom' [54]. The incidence of inadequate seizure control using standard drug therapy is still up to 30 % in paediatric epileptic population [34]. In those cases, non-pharmacological treatments such as epilepsy surgery, vagal nerve stimulation, immunoglobulin and behavioural and dietary therapies should be readily considered [53].

Ketogenic diet (KD) is composed of fat to protein ratio of 3:1 to 4:1 plus carbohydrates (in grammes). The concept of dietary therapy has been introduced at the beginning of the twentieth century, but it has been reconsidered only in the last two decades as a valuable option among alternative treatments of DRE, mainly in children [23]. The principal indications are GLUT-1 deficiency syndrome (GLUT1DS) and pyruvate dehydrogenase complex deficiency (PDCD) [46]. Infantile spasms, Dravet syndrome and myoclonic-astatic epilepsy are epilepsy syndromes for which KD should be considered early in the therapeutic pathway.

Major prejudices about its side effects, difficult compliance and doubts on efficacy have been overcome thanks to publication of large cases series [22, 57, 59, 69].

KD availability varies among different centres according to the level of expertise, experience and knowledge about it as a therapeutic option. Although the number of patients undergoing KD has increased, numbers remain low also because of lack of referrals and funding [60].

Ketogenic diet is an individualised treatment

More liberal versions of dietary therapy exist beyond the classical KD and medium-chain triglyceride diet (MCT): the modified Atkins diet (MAD) and low glycemic index treatment (LGIT) [30, 50, 71].

In the classical KD, the long-chain fats (90 %) compose the major percentage of daily caloric requirement and the remaining 10 % is from proteins and carbohydrates combined. Calories are initially reduced to 80–90 % of daily recommendations for age and then gradually increased according to the patient's weight. Fluid supplementation is always recommended [46].

The MCT diet, described as more palatable, provides more ketones per calorie, allowing more carbohydrates and proteins inclusions and fewer calories from fats [35, 83].

The Atkins diet, classically used to reduce weight, allows the intake of fats and the restriction of carbohydrates. The MAD is 'modified' compared to Atkins diet as the 'induction phase' of diet limiting carbohydrates to the range of 15–20 g per day which is maintained indefinitely [44, 78] . This diet is probably the most suitable for adults, due to its use of household measures and unrestricted proteins [75].

In line with the established efficacy of KD in several specific conditions, the development of commercially available formulas provide a quick and complete fixed solution for administering KD. Also, they can be administrated via feeding tube in neurologically impaired patients or in children younger than 12 months of age [33].

The consensus study group recommended the use of low-carbohydrate multivitamin and mineral supplements during the course of diet therapy. Oral citrates, antacids, carnitine and laxatives are optional supplements, and there is no evidence for empiric use [46].

Beyond the diet subtype, timing of diet administration, pharmacotherapy and efficacy based on the electroclinical and etiological diagnosis and patient's tolerance have to be tailored on every patient. Aside from seizure reduction, neurobehavioral, cognitive [19, 29, 38, 64] and sleep improvement [13, 26] could influence the decision-making in the management and duration of the diet [76].

Ketogenic diet contraindications and limits

KD should be considered after two antiepileptic drug trials failure, with no age or gender specificity. Every patient must be screened for fatty acid transport and oxidation disorders for which KD is contraindicated (carnitine deficiency, beta-oxidation defects, pyruvate carboxylase deficiency and porphyria) [46]. Indeed, a patient with fat metabolism disorder may develop a severe alteration during fasting or KD setting.

There was no definitive consensus whether KD may be suitable also for patients with surgical resectable region, as partial seizures were considered less responsive to KD than generalised seizures [46]. But there is now evidence in literature on how KD could be a valuable additional non-invasive option even in patients with focal malformation of cortical development [15, 69].

'Fine-tune' of ketogenic diet

Great variability in the course, timing and response to KD exists. Although 3 months has always been considered the minimum time frame to define whether KD is effective [46], a diet implementation up to 6 months can be considered to ascertain either quantitative or qualitative response. Before achieving a stable positive or negative response to the diet, neurologists and dieticians often attempt to 'fine-tune' the KD and improve seizure control. Retrospective studies have tried to identify most frequent modifications and their influence, and a trend towards medication adjustments being more successful than dietary modifications has been outlined [76]. A recent study evaluated the impact of an intermitting fasting regimen on children having an incomplete response to KD, showing transient further seizure reduction [31].

Many children are on multiple medications at diet onset. Among the interventions that might potentiate KD efficacy, drug modifications are often done as a final option; in fact, specific indications on how to cope with anticonvulsant pharmacotherapy during KD are lacking. In a retrospective study, Kossoff et al. tried to assess whether medication reduction in the first month after starting KD had an advantage over a late taper [42]; all patients appeared to benefit equally and to well tolerate discontinuation even as early as the admission. Further accurate reporting of medication adjustments among patients on KD could guide physicians to better integrate anticonvulsant pharmacotherapy and KD in the future.

Several studies focused on the interaction between AED and KD. Despite valproic acid (VPA) in conjunction with KD was seen to be safe and well tolerated [61], latest publication showed that idiosyncratic interaction with high-fat dietary therapies can lead to apparent dietary treatment failure [34]. This could be explained by VPA selective inhibition of particular enzymes implicated in fatty acids beta-oxidation [79]. Lamotrigine significantly interferes with KD, reducing ketosis achievement if used concomitantly [86]. Specifically, for the subgroup of GLUT1DS patients requiring an anticonvulsant beyond KD, some AEDs have been investigated for possible interactions with GLUT1DS such as barbiturates, diazepam, chloral hydrate and ethanol, which are inhibitors of GLUT1 function in vitro and might potentiate the effects of GLUT1-mediated glucose transport in patients with GLUT1DS. No inhibitory effects were observed for carbamazepine and phenytoin, indicating that these might be preferable in GLUT1DS [41].

Ketogenic diet suspension and transition

KD discontinuation timing and methods are tailored on every patient's response. Among patients who had seizure control of more than 50 %, KD is typically discontinued after approximately 2 years, after weighting the risks and benefits.

Discontinuation is usually done gradually within 2 to 3 months by decreasing the ketogenic ratio and re-introducing carbohydrates. Despite the lack of evidence on the ideal weaning timing, a retrospective study demonstrated no significant increase in risk of seizure exacerbation with rapid KD discontinuation (less than 6 weeks). Patients who achieved a seizure reduction of 50–99 % and those who were on polytherapy had the highest risk overall [90]. Worsening of seizure frequency or severity is carefully monitored this time [35].

Martinez et al. analysed retrospectively the seizure control after discontinuation of KD in patients achieving seizure freedom and found that the presence of recent EEG epileptiform activity, abnormal MRI, lower initial seizure frequency and tuberous sclerosis complex significantly increase the likelihood of recurrence [63].

Children with GLUT1DS and PDCD may require longer KD treatment. With GLUT1DS patients, seizure control is nearly complete without significant side effects; therefore, the diet can be maintained up to 6–12 years [35]. No information is available about the maximum duration.

In patients undergoing KD for long periods, the transition from paediatric to adult specialist requires proper attention and endorsement. What should be understood is also whether adolescents with milder forms of GLUT1DS could safely discontinue the diet before adulthood. Multidisciplinary centres worldwide will be needed to provide adequate transition options [49].

Not only for GLUT1DS patients, further studies with longer follow-up will be required to describe efficacy, tolerability, duration of the treatment, as well as the prognosis after discontinuation, taking into account epileptic syndromes.

Side effects

Adverse effects may occur and should be monitored. However, most of the adverse effects such as metabolic abnormalities, gastrointestinal (GI) symptoms and nutritional deficiencies are preventable and proved to be treatable.

Immediate, short-term and long-term side effects have to be differentiated. Fasting is now considered optional, and many centres no longer fast children at diet initiation. Immediate side effects (hypoglycaemia, dehydration, acidosis and lethargy) are seen less commonly when a non-fasting approach is utilised [2]. The most common short-term side effects are GI symptoms (nausea, vomiting, diarrhoea and constipation) which may lead to poor compliance affecting the efficacy. High-fat diet prolongs gastric emptying causing disturbances, especially in patients with gastro-oesophageal reflux, which is a common characteristic in epileptic patients. Constipation might be consequential to a decreased intake of fibres and may be more severe in children with neurologic impairment leading to low mobilisation. Importantly, many children present GI disturbances before starting the diet, and exacerbations or reversal have been reported [36].

Dyslipidaemia is a common adverse effect. However, children undertaking KD can metabolise the higher fat and cholesterol provided by the KD over time. Many discordant data exist regarding lipid profile changes: some studies refer about modest HDL reduction, others about an ApoB increase and others report stable levels of both LDL and HDL cholesterol (LDL-C; HDL-C). Moreover, children receiving a formula-only KD did have lower total cholesterol than those on solid KD [6, 23, 36, 70]. A study on the effect of KD on vascular function found a gradual decrease in carotid distensibility and an increase in LDL-C, ApoB and triglycerides: LDL-C and LDL-C to HDL-C ratios were seen at 3 and 12 months, but these differences appeared to be reversible and not significant after 24 months of treatment [37].

Rare early-onset complications previously described are as follows: hypertriglyceridemia, transient hyperuricemia, hypercholesterolemia, infectious diseases, symptomatic hypoglycaemia, hypoproteinaemia, hypomagnesemia, acute pancreatitis and persistent metabolic acidosis.

Long-term side effects including kidney stones, decreased linear growth, excessive weight loss, vitamin deficit and alterations in body composition could potentially occur with higher prevalence than short-term side effects.

Despite there are controversial data regarding body growth and bone density changes in patients treated with KD [3, 68, 82, 28], several reports showed poor linear growth, but the mechanism has not been clearly elucidated. GLUT1DS patients are the best candidates for studies with this aim, being their follow-up one of the longest. A recent case series on GLUT1DS adult patients treated with KD for more than 5 years demonstrated no major negative effects on body composition, bone mineral content and bone mineral density [4].

Hypoproteinaemia during KD is common; however, the underlying aetiologies have not been completely understood. Only one case of protein-losing enteropathy during the KD has been reported [66].

The impact of KD on arterial morphology, endothelial function and on cardiac diastolic function has also been evaluated in a cohort of epileptic children and young adults. In particular, arterial stiffness is increased before the increase of the intima media thickness, supporting that arterial stiffness is an early marker of vascular damage [14].

Prevention of nutrition-related side effects may be achieved through appropriate vitamins and minerals supplementation such as calcium, carnitine, selenium, zinc and vitamin D. Supplements should be carbohydrate-free. Until some years ago, there was a concrete risk of developing renal stones during KD; potassium citrate supplement, together with recommended fluid intake, is now often adopted as preventive agent [65].

Recently, the effects of a 12-week KD on inflammatory status, adipose tissue activity biomarkers, abdominal visceral and subcutaneous fat in children affected by GLUT1DS were evaluated. Results suggested that over a short period of time, KD does not affect inflammatory cytokines production and abdominal fat distribution [5]. Once again, more effective long-term studies are needed.

Old versus new ketogenic diet

The principal shortcoming in KD studies is the lack of a control group due to the fact that KD is traditionally reserved as the last treatment option after establishment of drug resistance. One double-blind study [24] and few randomised controlled trials have been published up to now [55, 69]. More specifically, Lambrecht et al. provided evidence that KD is effective compared to care as usual and Neal et al. studied the benefits of KD-treated group compared to no change in treatment in the control group, with the former seeing mean seizure frequency falling to 62 % and the latter seeing an increase to 137 % of seizure frequency compared to baseline. An example with direct comparison of a specific antiepileptic drug (ACTH) and KD in infantile spasms is present [45].

KD is the treatment of choice for two distinct disorders of brain metabolism: GLUT1DS and PDCD [3]. It is proved to be effective and safe as an early treatment for infantile spasms. A positive response has also been demonstrated in myoclonic-astatic epilepsy (Doose syndrome) [8], severe myoclonic epilepsy of infancy (Dravet syndrome) [7, 87], tuberous sclerosis complex [43] and Rett syndrome [76]. Moreover, a beneficial effect was seen in selected mitochondrial disorders, glycogenosis type V, Landau-Kleffner syndrome, Lafora body

disease [12] and subacute sclerosing panencephalitis [46]. Patients with focal, partial epilepsies appeared to have a reduced relative chance to obtain seizure freedom overall, especially if they have a localised lesion suitable for epilepsy surgery [56]. But, new reports in literature are describing good response to KD even in patients with focal malformation of cortical development [15, 69] (Table 1). Finally, refractory status epilepticus may become an indication [47].

As far as the international practise of KD is concerned, first and unique successful international consensus statement to identify shared attitudes in the clinical use of the KD dates to 2009, with 26 neurologists and dieticians from KD centres worldwide taking part in it [46].

Recently, a document outlining core requirements needed for a KD service has been published. This is to ensure the possibility of a broader network of KD and to make more accessible formulas and methods both for medical doctors and patients in new ketogenic diet (KD) centres in resource-limited regions of the world [52].

Old protocols have been revisited achieving optimal compliance and reduction of side effects up to zero. Fasting initiation is now considered optional; in selected patients, KD is now started without hospitalisation, and importantly, a normocaloric diet rather than hypocaloric diet has also been formulated.

Finally, challenging attempts to optimise KD use have been made in the direction of specific epileptic syndromes as epilepsy of infancy with migrating focal seizures and encephalopathy with status epilepticus during sleep (ESES). KD is also a well-tolerated treatment option for patients with ESES syndrome, with or without structural anomalies [10, 73].

New targets: ketogenic diet as a therapeutic option for refractory status epilepticus

Standard treatments for status epilepticus include intravenous antiepileptic medications and coma-inducing agents. Unfortunately, a significant subset of patients does not

Table 1 Comparison of "Old" and "New" ketogenic treatment approach

	Old	New
Qualified patients	Drug-resistant epilepsy Paediatric population	GLUT1DS [38]; PDCD [46]; MAE [8]; DS [87]; TSC [43]; RS [76]; MD; Glycogenosis type V; LKS; LBD [12]; SSP [46]; FE; encephalitis; FIRES [48]; glioma [67]; neurodegenerative diseases [81] Also adolescent and adults [62, 80]
Initiation	Mandatory hospitalisation 12–48 h fasting Fluid restriction	Outpatient and Inpatient initiation [56, 84] Fasting is optional [3, 39, 89] Increased fluid intake [46]
Diet type	Classic 4:1 KD	Different ratios of classic KD (4:1 3:1 2:1) MCT–MAD–LGIT
Daily caloric requirement	Limited (strict hypocaloric)	Adjusted for age, weight and activity [84]
AEDs management	No guidelines available	No guidelines available Suggested tailor-made management [76]
Follow-up	Urine ketones monitoring	Blood ketones monitoring [85]
Predictors of efficacy	Any predictor of efficacy available	Recent studies on EEG and clinical response [58, 88]
Neuropsychological/behavioural response	Potential [58]	Evaluated [9, 21]
Side effects (SE)	Addressing the side effects late Fasting SE (ie., hypoglycaemia, lethargy, dehydration) Rare long-term SE (early discontinuation)	Prevention rather than correction (introduction of supplements*) [25, 65] No fasting SE Long-term SE (discordance and lack of strong data) [4, 68]
Compliance rate	Poor	Improved [35]
Discontinuation	At least 2 weeks	At least 3 months [51]
Transition	No programme available	Programme available but not yet implemented [49, 51]

GLUT1DS GLUT1 deficiency syndrome, *PCDC* pyruvate dehydrogenase complex deficiency, *MAE* myoclonic-astatic epilepsy, *DS* Dravet syndrome, *TSC* tuberous sclerosis complex, *RS* Rett syndrome, *MD* mitochondrial disorders, *LKS* Landau-Kleffner syndrome, *LBD* Lafora body disease, *SSP* subacute sclerosing panencephalitis, *FE* focal epilepsy, *FIRES* fever-induced refractory epileptic encephalopathy

*Potassium citrate, calcium, carnitine, selenium, zinc, vitamin D

respond to conventional therapies. The largest study of KD for refractory status epilepticus (RSE) is by Nabbout et al., who retrospectively examined the use of KD for RSE secondary to fever-induced refractory epileptic encephalopathy (FIRES). The KD was started using various formulas via nasogastric tubes, and glucose was removed from both medications and intravenous fluids. Within a mean of 2.8 days, all but one of the eight children developed ketonuria and, remarkably, seven of these eight children rapidly responded to KD [47].

Data until now (more than 30 patients) suggest that the KD is a reasonable and safe option for treatment of RSE with immunomediated causes (encephalitis and FIRES) [48]. Early consideration of KD in the management of RSE seems safe and well tolerated, with no demonstrated interactions with antibiotics or AEDs, and a possible anti-inflammatory action has been suggested [26].

Moreover, a report of two paediatric patients with refractory myoclonic status epilepticus showed improvement in seizure control with KD for a minimum follow-up of at least 6 months [11].

Cases of severe RSE have also been proposed to be responsive to KD. However, more prospective, randomised controlled trials studies are needed to conclusively evaluate its efficacy and eventually determine the optimal protocol for KD initiation.

New targets of neuropharmacology

The concept that KD may be neuroprotective brought to a broader coverage of its use in epilepsy but might also have an implication in neurodegenerative or metabolic derangement [74, 81]. An experimental study on a rodent model of epilepsy has been utilised—the KCNA1-null mutant mouse—and ketone bodies effects on mitochondrial permeability transition (mPT) were tested. Data revealed that the first direct link between mPT and seizure control provides a potential mechanism for the KD action through the cyclophilin D subunit of the mPT complex. Given that mPT is increasingly being implicated in diverse neurological disorders, these results suggest that metabolic substrates might represent a worthy paradigm for therapeutic development [40].

The potential the anti-inflammatory action of KD is acquiring more relevance. Data suggest that exploiting cellular mechanisms associated with ketone-based metabolism offers new therapeutic opportunities for controlling pain and peripheral inflammation [20].

A potential anti-seizure role of dietary protein or individual amino acids in the KD has been hypothesised. Hartman et al. study raises the possibility that D-leucine may represent a new class of anti-seizure agents [32].

Lastly, neuroactive peptides could play a role in modulating epileptic activity. Des-acyl ghrelin, which is increased in catabolic states, had an anticonvulsant activity in status epilepticus animal model. A des-acyl ghrelin analogue, EP-80,317, was also effective in preventing seizure induction by pilocarpine when preventively administered in rats [27].

Now that a plateau has been reached in terms of clinical understanding of KD application, clarification of neuronal and molecular mechanisms of its effects is crucial.

New targets: ketogenic diet and cancer

The reason why KD could be used with cancer derives from the evidence that cancer cells, unlike normal cells, are unable to use ketone bodies because of their altered oxidative phosphorylation [77]. This potential of KD has been investigated mainly in animal models of brain tumours. For example, the growth of malignant astrocytoma and glioblastoma xenografts in mice was inhibited significantly by a calorie-restricted KD, which also had significantly enhanced the antitumour effect of radiation therapy in glioma patients [1]. A recent publication by Schwartz et al. reported the experience of two glioma patients undergoing an energy-restricted KD that resulted effective in controlling the progression of some gliomas and had no major side effects. Finally, neuroblastoma showed up as a potential target of KD adjuvant therapy [67].

Compliance and ketogenic diet economics

Compliance is crucial in validating KD therapy and involves patients, families and caregivers. Meals preparation can be burdensome for parents and caregivers and requires great attention. Moreover, KD-positive effects may appear slowly and not satisfactorily. That is why compliance should be continuously assessed during follow-up, in order to be sure that KD efficacy can be properly evaluated. In the specific set of GLUT1DS patients, where KD is exclusively efficacious, compliance has proved to be much better than in other conditions for which KD is indicated [16].

Sometimes, in order to ameliorate compliance, KD ratios can be lowered by implementation of carbohydrates. At present, its palatability is somehow improving and more KD-based formula, although expensive, are readily available.

A recent study has evaluated KD cost-effectiveness compared with care as usual (CAU) in patients with intractable epilepsy; despite seizure reduction, KD showed to have an unfavourable cost per QALY ratio [18]. A previous study showed that compared to vagal nerve stimulation (VNS), which constitutes a valid non-pharmacologic alternative for intractable epilepsy, KD is more effective and less costly, after 12 months [17]. Indeed, when coping with intractable

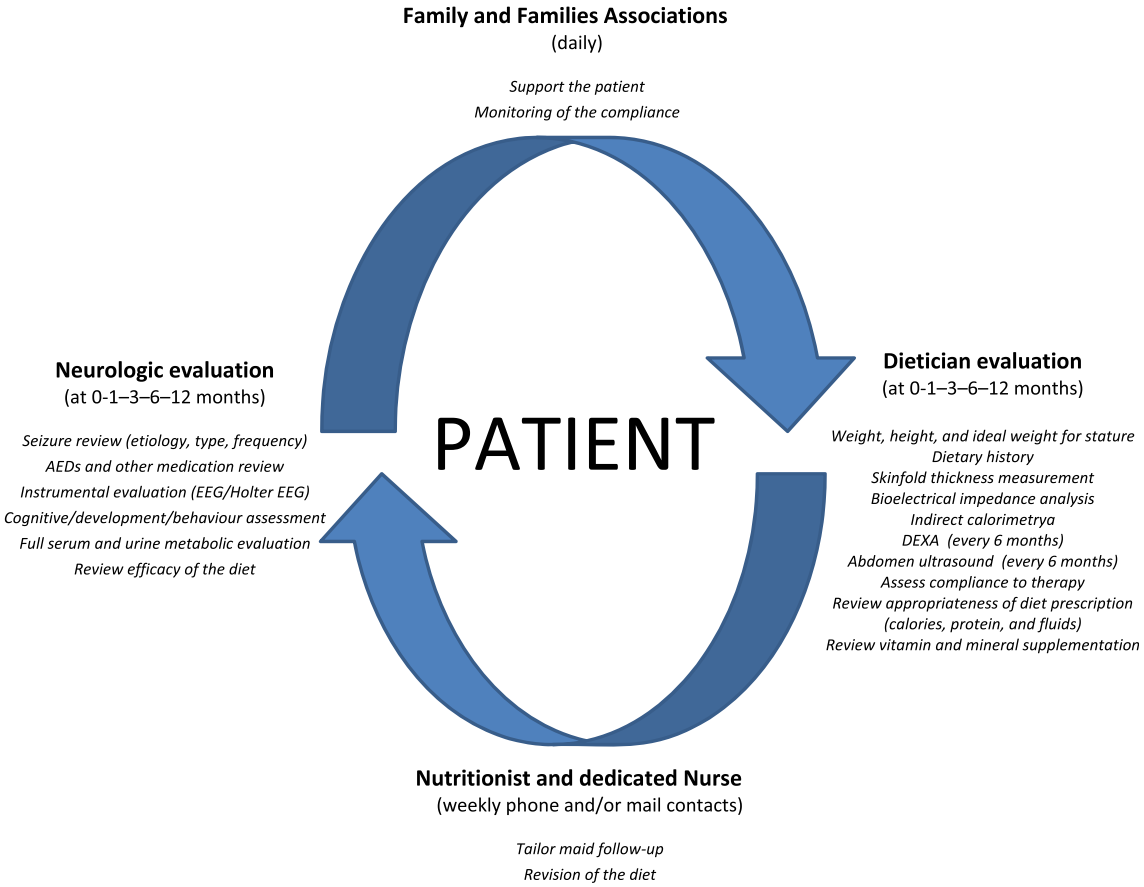

Fig. 1 A proposed multidisciplinary approach for tailor-made Ketogenic Diet for drug-resistant epilepsy

epilepsy, both KD and VNS compared to CAU resulted to be more effective but also more expensive.

Ketogenic diet in European countries versus the world

As to our experience in Italy, KD is still underutilised and does not stand as a properly known alternative for many child neurologists and epileptologists. This could influence data availability about the effective response to KD. Even if there are no data yet showing a positive correlation to early implementation of KD, we know that epilepsy refractoriness and encephalopathies are likely to become more severe if not properly managed.

It could be extremely beneficial to have a European consensus, in addition to the international consensus [46], and national protocols [87], in order to better deal with the local needs and to reinforce a multidisciplinary approach (Fig. 1) to KD, not to be easily found.

And along with a more consolidated multidisciplinary approach, family associations on KD are to be greatly encouraged as they represent an important factor providing social support and awareness. It would therefore be advisable to set a European net of medical centres promoting KD and social support.

Conclusions

Inefficient connectivity and big differences in KD management and proposal worldwide are still a considerable obstacle.

Moreover, large regions of the world do not have widespread availability of KD (e.g., Caribbean, Central America, Africa, Eastern Europe and Southeast Asia regions). The reason for that is likely to be found in poor and heterogeneous availability of KD teams, dietetic and formula supplements and even appropriate food [52].

It is very crucial to stay focused on the importance of KD as a valid alternative treatment for DRE and, more in general, on the correct management of intractable epilepsy. Adequate non-pharmacologic choices should be prospected earlier in the therapeutic pathway, in order to change or arrest disease course. There should be then more awareness about the sanitary costs due to frequent hospitalizations, expensive drugs and highly specialised multidisciplinary medical teams.

Even social and affective consequences are to be kept in mind when deciding for a therapeutic intervention in DRE.

Also, although no prospective studies of developmental or behavioural outcomes have been performed so far, anecdotal evidence and parental reports have indicated that children treated with KD show increased alertness and better cognitive functioning, as well as improved behaviour [25, 29, 72, 21]. Maybe, focusing only on seizure control may not express the full range of KD potential.

More precise tuning and understanding of KD should be continuously searched in order to give more information and expectancy to families.

Current research on KD mechanism of action could show new insights in re-evaluating cerebral metabolism and in applying KD also to neurologic conditions other than epilepsy and thus exploring new populations.

And future perspectives, both for epilepsy and cancer application of KD, might be the use of novel metabolomics and proteomic technologies, still unexplored with patients undergoing KD.

Acknowledgments We would also like to thank the A.I.E.F. ONLUS Foundation, Associazione Italiana GLUT1 for their support. Also, we extend our gratitude to Simona Lunghi, Grazia Papalia, Marco Fasce and Massimiliano Tumminelli for their essential assistance and technical support.

Authors' contribution Ludovica Pasca: data collection, drafting and revising the manuscript;

Valentina De Giorgis: data collection; drafting and revising the manuscript

Joyce Ann Macasaet: drafting

Claudia Trentani: revising the manuscript

Anna Tagliabue: revising the manuscript

Pierangelo Veggiotti: data collection; interpretation of the data; revising the manuscript

Compliance with ethical standards All the Authors have read and approved the submission of the manuscript, in which the material has not been published and is not being considered for publication elsewhere in whole or in part in any language. All the authors meet the appropriate authorship criteria; nobody who qualifies for authorship has been omitted from the list. Authors' contribution and funding sources have been properly acknowledged, and the authors approved the acknowledgement of their contribution. All the authors have full access to all of the data that support the publication.

I confirm that my manuscript complies with the ethical rules applicable for this journal.

Conflict of interest The authors declare that they do not have any conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

I confirm that the manuscript does not report any data collected from humans or animals and does not involve human participants and reporting health related outcomes.

I confirm that I have read journal's guidance on competing interests and I confirm that none of the authors have any competing interests in the manuscript.

References

1. Abdelwahab MG, Fenton KE, Preul MC, Rho JM, Lynch A, Stafford P, Scheck AC (2012) The ketogenic diet is an effective adjuvant to radiation therapy for the treatment of malignant glioma. PLoS 7(5):e36197
2. Bergqvist C, Schall JI, Gallagher PR, Cnaan A, Stallings V (2005) Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. Epilepsia 46:1810–1819
3. Bergqvist AG, Schall JI, Stallings VA, Zemel BS (2008) Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. Am J Clin Nutr 88(6):1678–1684
4. Bertoli S, Trentani C, Ferraris C, De Giorgis V, Veggiotti P, Tagliabue A (2014) Long-term effects of a ketogenic diet on body composition and bone mineralization in GLUT-1 deficiency syndrome: a case series. Nutrition 30(6):726–728
5. Bertoli S, Neri IG, Trentani C, Ferraris C, De Amicis R, Battezzati A, Veggiotti P, De Giorgis V, Tagliabue A (2015) Short-term effects of ketogenic diet on anthropometric parameters, body fat distribution, and inflammatory cytokine production in GLUT1 deficiency syndrome. Nutrition 31(7–8):981–987
6. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T (2013) Very-low-carbohydrate ketogenic diet v. Low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr 110(7):1178–1187
7. Caraballo RH, Cersosimo RO, Sakr D, Cresta A, Escobal, Fejerman N (2005) Ketogenic diet in patients with Dravet syndrome. Epilepsia 46:1539–1544
8. Caraballo RH, Cersosimo RO, Sakr D, Cresta A, Escobal N, Fejerman N (2006) Ketogenic diet in patients with myoclonic-astatic epilepsy. Epileptic Disord. 8:151–155
9. Caraballo R, Vaccarezza M, Cersósimo R, Rios V, Soraru A, Arroyo H, Agosta G, Escobal N, Demartini M, Maxit C, Cresta A, Marchione D, Carniello M, Paníco L (2011) Long-term follow-up of the ketogenic diet for refractory epilepsy: multicenter Argentinean experience in 216 pediatric patients. Seizure 20: 640–645
10. Caraballo RH, Noli D, Cachia P (2015) Epilepsy of infancy with migrating focal seizures: three patients treated with the ketogenic diet. Epileptic Disord. 17:194–197
11. Caraballo RH, Reyes G, Armeno M, Fortini S, Mestre G, Cresta A (2015) The ketogenic diet in two paediatric patients with refractory myoclonic status epilepticus. Epileptic Disord 17:491–495
12. Cardinali S, Canafoglia L, Bertoli S, Franceschetti S, Lanzi G, Tagliabue A (2006) A pilot study of a ketogenic diet in patients with Lafora body disease. Epilepsy Res 69(2):129–134
13. Coppola G, Klepper J, Ammendola E, Florillo M, della Corte R, Capano G, Pascotto A (2006) The effects of the ketogenic diet in refractory partial seizures with reference to tuberous sclerosis. Eur J Paediatr Neurol 10:148–151
14. Coppola G, Natale F, Torino A, Capasso R, D'Aniello A, Pironti E, Santoro E, Calabrò R, Verrotti A (2014) The impact of the ketogenic diet on arterial morphology and endothelial function in children and young adults with epilepsy: a case-control study. Seizure 23(4): 260–265
15. Da Eun Jung DE, Kang HC, Kim HD (2008) Long-term outcome of the ketogenic diet for intractable childhood epilepsy with focal malformation of cortical development. Pediatrics 122(2):e330–e333
16. De Giorgis V, Veggiotti P (2013) GLUT1 deficiency syndrome 2013: current state of the art. Seizure 22:803–811
17. De Kinderen RJ, Postulart D, Aldenkamp AP, Evers SM, Lambrechts DA, de Louw A, Majoie MH (2015) Cost-effectiveness of the ketogenic diet and vagus nerve stimulation for the treatment of children with intractable epilepsy. Epilepsy Res 110:119–131

18. De Kinderen RJ, Lambrechts DA, Wijnem BF, Postulart D, Aldenkamp AP, Majoie MH, Evers SM (2016) An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: an interim analysis. Epilepsia 57:41–50
19. Dressler A, Stocklin B, Reithofer E, Benninger F, Freilinger M, Hauser E, Reiter-Fink E, Seidl R, Trimmel-Schwahofer P, Feucht M (2010) Long-term outcome and tolerability of the ketogenic diet in drug- resistant childhood epilepsy—the Austrian experience. Seizure 19:404–408
20. Dupuis N, Curatolo N, Benoist JF, Auvin S (2015) Ketogenic diet exhibits anti-inflammatory properties. Epilepsia 56(7):e95–e98
21. Farasat S, Kossoff EH, Pillas DJ, Rubenstein JE, Vining EP, Freeman JM (2006) The importance of parental expectations of cognitive improvement for their children with epilepsy prior to starting the ketogenic diet. Epilepsy Behav 8:406–410
22. Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM (1998) The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics 102(6):1358–1363
23. Freeman JM, Kossoff EH, Hartman AL (2007) The ketogenic diet: one decade later. Pediatrics 119(3):535–543
24. Freeman JM, Vining EP, Kossoff EH, Pyzik PL, Ye X, Goodman SN (2009) A blinded, crossover study of the efficacy of the ketogenic diet. Epilepsia 50:322–325
25. Freeman J, Veggiotti P, Lanzi G, Tagliabue A, Perucca E (2006) The ketogenic diet: from molecular mechanisms to clinical effects. Epilepsy Res 68:145–180
26. Fung EL, Chang SK, Yam KK, Yau PY (2015) Ketogenic diet as a therapeutic option in super-refractory status epilepticus. Pediatr Neonatol 56(6):429–431
27. Giordano C, Marchiò M, Timofeeva E, Biagini G (2014) Neuroactive peptides as putative mediators of antiepileptic ketogenic diets. Front Neurol 5:63
28. Groesbeck DK, Bluml RM, Kossoff EH (2006) Long-term use of the ketogenic diet in the treatment of epilepsy. Dev Med Child Neurol 48(12):978–981
29. Hallböök T, Ji S, Maudsley S, Martin B (2012) The effects of the ketogenic diet on behavior and cognition. Epilepsy Res 100: 304–309
30. Hartman AL, Vining EP (2007) Clinical aspects of the ketogenic diet. Epilepsia 48:31–42
31. Hartman AL, Rubenstein JE, Kossoff EH (2013) Intermittent fasting: a 'new' historical strategy for controlling seizures? Epilepsy Res 104:275–279
32. Hartman AL, Santos P, O'Riordan KJ, Stafstrom CE, Hardwick JM (2015) Potent anti-seizure effects of D-leucine. Neurobiol Dis 82: 46–53
33. Hosain SA, La-Vega-Talbott M, Solomon GE (2005) Ketogenic diet in pediatric epilepsy patients with gastrostomy feeding. Pediatr Neurol 32:81–83
34. Hughes I, Russo K, Wang D (2015) Idiosyncratic interactions between the ketogenic diet and valproic acid: a case series. Neurology 84:2478
35. Huttenlocher PR, Wilbourn AJ, Signore JM (1971) Medium-chain triglycerides as a therapy for intractable childhood epilepsy. Neurology 21:1097–1103
36. Kang HC, Chung DE, Kim DW, Kim HD (2004) Early and late onset complications of the ketogenic diet for intractable epilepsy. Epilepsia 45:1116–1124
37. Kapetanakis M, Liuba P, Odermarsky M, Lundgren J, Hallbook T (2014) Effects of ketogenic diet on vascular function. Eur J Paediatr Neurol 18(4):489–494
38. Kass HR, Winesett SP, Bessone SK, Turner Z, Kossoff E (2016) Use of dietary therapies amongst patients with GLUT1 deficiency syndrome. Seizure 14:83–87
39. Kim DW, Kang HC, Park JC, Kim HD (2004) Benefits of the nonfasting ketogenic diet compared with the initial fasting ketogenic diet. Pediatrics 114(6):1627–1630
40. Kim do Y, Simeone KA, Simeone TA, Pandya JD, Wilke JC, Ahn Y, Geddes JW, Sullivan PG, Rho JM (2015) Ketone bodies mediate antiseizure effects through mitochondrial permeability transition. Ann Neurol 78(1):77–87
41. Klepper J, Florcken A, FIschbarg J, Voit T (2003) Effects of anticonvulsants on GLUT1-mediated glucose transport in GLUT1 deficiency syndrome in vitro. Eur J Pediatr 162:84–89
42. Kossoff EH, Pyzik PL, McGrogan JR, Rubenstein JE (2004) The impact of early versus late anticonvulsant reduction after ketogenic diet initiation. Epilepsy Behav 5:499–502
43. Kossoff EH, Thiele EA, Pfeifer HH, McGrogan JR, Freeman JM (2005) Tuberous sclerosis complex and the ketogenic diet. Epilepsia 46:1684–1686
44. Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP (2006) A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. Epilepsia 47:421–424
45. Kossoff EH, Hedderick EF, Turner Z, Freeman JM (2008) A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. Epilepsia 49:1504–1509
46. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, Buchhalter JR, Caraballo RH, Helen Cross J, Dahlin MG, Donner EJ, Klepper J, Jehle S, Kim HD, Christiana Liu YM, Nation J, Nordli DR, Pfeifer HH, Rho JM, Stafstrom CE, Thiele EA, Turner Z, Wirrell EC, Wheless JW, Veggiotti P, Vining EP, Charlie Foundation, Practice Committee of the Child Neurology Society, Practice Committee of the Child (2009) Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group. Epilepsia 50:304–317
47. Kossoff EH (2011) The fat is in the fire: ketogenic diet for refractory status epilepticus. Epilepsy Curr 11:88–89
48. Kossoff EH, Nabbout R (2013) Use of dietary therapy for status epilepticus. J Child Neurol 28(8):1049–1051
49. Kossoff EH, Henry BJ, Cervenka MC (2013) Transitioning pediatric patients receiving ketogenic diets for epilepsy into adulthood. Seizure 22:487–489
50. Kossoff EH, Wang H-S (2013) Dietary therapies for epilepsy. Biomed J 36:2–8
51. Kossoff EH, Veggiotti P, Genton P, Desguerre I (2014) Transition for patients with epilepsy due to metabolic and mitochondrial disorders. Epilepsia 55:37–40
52. Kossoff EH, Al-Macki N, Cervenka MC, Kim HD, Liao J, Megaw K, Nathan JK, Raimann X, Rivera R, Wiemer-Kruel A, Williams E, Zupec-Kania B (2015) What are the minimum requirements for ketogenic diet services in resource-limited regions? Recommendations from the International League Against Epilepsy Task Force for Dietary Therapy. Epilepsia 56(9):1337–1342
53. Kwan P, Brodie MJ (2000) Early identification of refractory epilepsy. N Engl J Med 342:314–319
54. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51:1069–1077
55. Lambrechts DA, de Kinderen RJ, Vles JS, de Louw AJ, Aldenkamp AP, Majoie HJ (2016) A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand. Mar 29
56. Lee PR, Kossoff EH (2011) Dietary treatments for epilepsy: management guidelines for the general practitioner. Epilepsy Behav 21: 115–121
57. Levy RG, Cooper PN, Giri P (2012) Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev 14(3): CD001903

58. Li BM, Tong LL, Jia GJ, Wang JW, Lei GF, Yin P, Sun RP (2013) Influence of ketogenic diet on the clinical effects and electroencephalogram features in 31 children with pharmacoresistant epileptic encephalopathy. Zhonghua Er Ke Za Zhi 51(5):362–366
59. Li HF, Zou Y, Ding G (2013) Therapeutic success of the ketogenic diet as a treatment option for epilepsy: a meta-analysis. Iran J Pediatr 23:613–620
60. Lord K, Magrath G (2010) Use of the ketogenic diet and dietary practices in the UK. J Hum Nutr Diet 23:126–132
61. Lyczkowski DA, Pfeifer HH, Ghosh S, Thiele EA (2005) Safety and tolerability of ketogenic diet in pediatric epilepsy: effects of valproate combination therapy. Epilepsia 46(9):1533–1538
62. Mady MA, Kossoff EH, McGregor AL, Wheless JW, Pyzik PL, Freeman JM (2003) The ketogenic diet: adolescents can do it too. Epilepsia 44:847–851
63. Martinez CC, Pyzik PL, Kossoff EH (2007) Discontinuing the ketogenic diet in seizure-free children: recurrence and risk factors. Epilepsia 48:187–190
64. Maydell BV, Wyllie E, Akhtar N, Kotagal P, Powaski K, Cook K, Weinstock A, Rothner AD (2001) Efficacy of the ketogenic diet in focal versus generalized seizures. Pediatr Neurol 25(3):208–212
65. McNally MA, Pyzik PL, Rubenstein JE, Hamdy RF, Kossoff EH (2009) Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet. Pediatrics 124(2):e300–e304
66. Moriyama K, Watanabe M, Yamada Y, Shiihara T (2015) Protein-losing enteropathy as a rare complication of the ketogenic diet. Pediatr Neurol 52(5):526–528
67. Morscher RJ, Aminzadeh-Gohari S, Feichtinger RG, Mayr JA, Lang R, Neureiter D, Sperl W, Kofler B (2015) Inhibition of neuroblastoma tumor growth by ketogenic diet and/or calorie restriction in a CD1-Nu mouse model. PLoS One 10(6):e0129802
68. Nation J, Humphrey M, MacKay M, Boneh A (2014) Linear growth of children on a ketogenic diet: does the protein-to-energy ratio matter? J Child Neurol 29(11):1496–1501
69. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross JH (2008) The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 7(6):500–506
70. Nizamuddin J, Turner Z, Rubenstein JE, Pyzik PL, Kossoff EH (2008) Management and risk factors for dyslipidemia with the ketogenic diet. J Child Neurol 23:758–761
71. Pfeifer HH, Thiele EA (2005) Low-glycemic-index treatment: a liberalized ketogenic diet for treatment of intractable epilepsy. Neurology 65:1810–1812
72. Pulsifer MB, Gordon JM, Brandt J, Vining EP, Freeman JM (2001) Effects of ketogenic diet on development and behavior: preliminary report of a prospective study. Dev Med Child Neurol 43:301–306
73. Reyes G, Flesler S, Armeno M, Fortini S, Ariela A, Cresta A, Mestre G (2015) Ketogenic diet in patients with epileptic encephalopathy with electrical status epilepticus during slow sleep. Epilepsy Res 113:126–131
74. Rho JM, Stafstrom CE (2012) The ketogenic diet: what has science taught us? Epilepsy Res 100:210–217
75. Schoeler NE, Cross H (2016) Ketogenic dietary therapies in adults with epilepsy: a practical guide. Pract Neurol 16:208–214
76. Selter JH, Turner Z, Doerrer SC, Kossoff EH (2014) Dietary and medication adjustments to improve seizure control in patients treated with the ketogenic diet. J Child Neurol 30(1):53–57
77. Seyfried TN, Sanderson TM, El-Abbadi MM, McGowan R, Mukherjee P (2003) Role of glucose and ketone bodies in the metabolic control of experimental brain cancer. Br J Cancer 89: 1375–1382
78. Sharma S, Jain P (2014) The modified Atkins diet in refractory epilepsy. Epilepsy Res Treat 2014:404202
79. Silva MF, Ruiter JP, IJIst L, Jakobs C, Duran M, de Almeida IT, Wanders RJ (2001) Differential effect of valproate and its Delta2- and Delta4-unsaturated metabolites, on the beta-oxidation rate of long-chain and medium-chain fatty acids. Chem Biol Interact 137(3):203–212
80. Sirven J, Whedon B, Caplan D, Liporace J, Glosser D, O'Dwyer J, Sperling MR (1999) The ketogenic diet for intractable epilepsy in adults: preliminary results. Epilepsia 40:1721–1726
81. Stafstrom CE, Rho JM (2012) The ketogenic diet as a treatment paradigm for diverse neurological disorders. Front Pharmacol 3:1–8
82. Tagliabue A, Bertoli S, Trentani C, Borrelli P, Veggiotti P (2012) Effects of the ketogenic diet on nutritional status, resting energy expenditure, and substrate oxidation in patients with medically refractory epilepsy: a 6-month prospective observational study. Clin Nutr 31(2):246–249
83. Trauner DA (1985) Medium-chain triglyceride (MCT) diet in intractable seizure disorders. Neurology 35:237–238
84. Vaisleib II, Buchhalter JR, Zupanc ML (2004) Ketogenic diet: outpatient initiation, without fluid or caloric restriction. Pediatr Neurol 31:198–202
85. Van Delft R, Lambrechts D, Verschuure P, Hulsman J, Majoie M (2010) Blood beta-hydroxybutyrate correlates better with seizure reduction due to ketogenic diet than do ketones in the urine. Seizure 19:36–39
86. Van der Louw EJ, Desadien R, Vehmeijer FO, Van der Sijs H, Castman_berrevoets CE, Neuteboom RF (2015) Concomitant lamotrigine use is associated with decreased efficacy of the ketogenic diet in childhood refractory epilepsy. Seizure 32:75–77
87. Veggiotti P, Burlina A, Coppola G, Cusmai R, De Giorgis V, Guerrini R, Tagliabue A, Bernardina BD (2011) The ketogenic diet for Dravet syndrome and other epileptic encephalopathies: an Italian consensus. Epilepsia 52:83–89
88. Walker I, Said RR (2014) Predictors of ketogenic diet efficacy in children based on the electroencephalogram. J Child Neurol 30(10): 1270–1274
89. Wirrell EC, Darwish HZ, Wirrell EC, Darwish HZ, Dyjur WC, Blackman M, Lange V (2002) Is a fast necessary when initiating the ketogenic diet? J Child Neurol 17:179–182
90. Worden LT, Turner Z, Pyzik PL, Rubenstein JE, Kossoff EH (2011) Is there an ideal way to discontinue the ketogenic diet? Epilepsy Res 95:232–236